Specific Aims

Aim 1: To test the hypothesis that youth with depressive disorders who are randomly assigned to the ROAD intervention compared to usual care (UC) will demonstrate improved depressive symptoms and psychosocial functioning at 6 and 12 months as shown by: decreased total depressive symptoms on the Children's Depression Rating Scale (CDRS-R); a higher proportion of youth with a 50% or more decrease in depressive symptoms; a higher proportion of youth in remission (defined as a CDRS-R total score $\leq$28) at each study time point; and improved peer, family and school functioning as demonstrated by a decrease in score on the Columbia Impairment Scale (CIS).

Aim 2: To test the hypothesis that youth who participate in the intervention compared to those in UC will be more likely to receive and adhere to evidence-based treatments for depression, including guideline-level antidepressant care (measured as proportion receiving a minimally effective dose for 3 months and/or psychotherapy (measured as proportion receiving at least 4 sessions (one complete module) of a brief cognitive behavioral therapy program).

Background/Significance

Between 1990 and 2000 the NIMH funded several randomized controlled trials to test collaborative care models versus usual care for depression in primary care in diverse health care systems and multiple geographic regions of the United States. The evidence from these trials that showed collaborative care models markedly improve quality of depression care and patient outcomes had an important ripple effect on stimulating private foundation and other government-supported research to further refine the model and test it in diverse settings with diverse populations. These highly successful trials, in combination with the earlier work, resulted in work summarizing studies and the effectiveness of the model, as well as the incorporation of these models into treatment guidelines and recommendations from groups like the U.S. Primary Care Preventive Task Force. This work, in turn, stimulated further foundation-funded research to enhance and disseminate the treatment model. Over the past few years, this large body of evidence has resulted in significant efforts to adopt this model on the part of health care delivery organizations and governmental bodies in the United States and around the world (such as the Veteran's Affairs Administration, the state of Maine, and Kaiser Permanente of Southern California).

The study of collaborative care in adolescents is in a similar position to where the adult field was in the early 1990's. Although results from the Youth Partner's in Care (YPIC) study are encouraging, intervention engagement was low and there was only a modest effect on depressive symptoms. More study is needed to examine models that focus on youth with major depression, who are most likely to require treatment, and that incorporate the latest evidence and guidelines for advancing treatment for youth who do not respond to initial therapy. Additionally, work is needed to create innovative strategies to engage adolescents and parents. The current study is designed to address these concerns and to continue to build the body of evidence needed to assure the growth of the field of adolescent depression treatment in primary care.

Our current study builds on the work of the YPIC study and expands the field by implementing new strategies that are designed to incorporate new evidence gathered since the YPIC study was conducted. The main differences between the current study and the YPIC study include: 1) a primary focus on youth with major depression (in the YPIC study 57% of the sample had subsyndromal depression); 2) implementation of a standardized stepped care algorithm to advance treatment (including the provision of combination treatment) and additional evaluation for youth who are not improving after 6-8 weeks of treatment as consistent with adult treatment models and the Guidelines for Adolescent Depression in Primary Care (GLAD-PC) treatment guidelines; 3) scheduled regular supervision of the depression care

manager with a team of child mental health experts to assist with implementation of the stepped care algorithm; and 4) increasing the duration of the care manager follow-up to one year to allow for increased focus on assuring continuation treatment. In focusing on these areas, the ROAD intervention also provides a consistent framework for implementing the GLAD-PC treatment guidelines.

This study is a randomized control trial designed to test a new collaborative care treatment program for Group Health adolescents with major depression. We have included detailed information about this process below.

Study Population:

Inclusion

Group Health Cooperative enrollees age of 13 years +0 months to 17 years + 10 months at the date of the data pull and meeting DSM-IV criteria for major depression, and/or
1)a PHQ-9 score of $\geq$10 with a CDRS score $\geq$ 42.

Exclusion

Youth will be excluded if their parents/guardians plan to disenroll from GHC during the 12 month study period or if their severity warrants specialty mental health care due to: 1) current alcohol or substance abuse as assessed by the CRAFFT (score of 5 or higher) or bipolar disorder., 2) high suicide risk, based on presence of a plan or recent attempt, 3) already regular treatment with a psychiatrist or psychiatric hospitalization in the prior year*, or 4) Self-reported history of pervasive developmental delay or autism. *Patients will not be excluded if they were prescribed antidepressants or other psychoactive medications as long as they meet inclusion and exclusion criteria. Additional exclusion criteria include: no telephone at home and inability of the adult and/or youth to communicate adequately in English.

Identification of Participants:

Youth will be invited to participate using the following protocol:

- Study participants will be identified from two pathways:
  - Analysts will use enrollment data to identify all adolescents with a primary care provider in each of the study clinic sites.
  - Physician/Provider Referrals (providers from participating clinics will be able to refer patients that they feel would benefit from participating in the study directly to ROAD study staff via email, phone, EMR messaging, or in-person contact.

2) Parents of all potential participants will receive a pre-screening advance letter to inform them of the study and the upcoming call with a number that they can call to refuse further contact.

3) Parents will receive a call from interviewers (either trained ROAD study staff or the Survey Research Program/SRP staff) and verbal consent will be obtained to interview the youth

4) The interviewer will obtain consent from the youth (during the same phone call if possible) and will administer the PHQ-2 by telephone.

5) All youth with a PHQ-2 screen of $\geq$2 (indicating the presence of depressed mood or anhedonia) will be asked to complete the remaining questions for the full PHQ-9.

6) All youth who screen positive on the PHQ-9 will be mailed information about the study. Screening interviewers will tell the potential participant to expect the information to arrive in the mail, and that ROAD study staff will follow-up with them after they have received it. Those screened as negative are thanked for their time.

7) ROAD study staff will make follow-up phone calls 5-7 days after the mailing, to answer any questions and to schedule the in-person baseline assessment interview in the primary care clinic. To screen out youth with temporary symptoms or brief adjustment disorders, baseline assessments will be scheduled

approximately 2 weeks following the screening assessment and the PHQ-9 will be repeated to confirm persistence of symptoms on a second screen.

8) At the baseline visit, all youth who meet DSM-IV criteria for major depression on the K-SADS or who continue to have a PHQ-9 ≥10 and a CDRS score ≥ 42 will be invited to participate in the intervention study.

Randomization and Intervention:

Following the completion of informed consent and the baseline assessment, we will randomize subjects to the ROAD intervention or to usual care (UC), followed within 1-2 weeks by a pre-treatment education and engagement session (only ROAD intervention patients).

Intervention content: The intervention incorporates key elements of collaborative care interventions (case management with regular supervision by mental health specialists and provision of evidence based treatments including medication and brief psychotherapy) that have been shown to improve quality and outcomes of depression treatment among adults in primary care and extends the model to better address the needs of adolescents and their families. Table 5 provides a brief overview of core components of the ROAD intervention including adaptations made to better address the needs of adolescent populations.

Table 2 – ROAD Intervention Overview

Core components of the collaborative care model in the ROAD intervention
• The provision of **care-management by a Depression Care Manager (DCM)** with mental health treatment experience with weekly assessment during the acute treatment phase and monthly assessment during the continuation phase • The provision of **weekly caseload supervision** by a team of mental health and pediatric specialists (psychiatrist, psychologist, and adolescent medicine specialist) • Development of an **Excel-based electronic registry** to facilitate caseload supervision • **Patient selection of evidence-based treatment** (psychotherapy or antidepressant medication) • **Stepped care algorithm** to advance treatment for patients who are not improving on their initial choice of treatment with the option of further psychiatric evaluation
Adaptations for working with adolescent populations
• The provision of **adolescent-specific educational materials** for youth and parents to reference as needed • The development of a **safety plan** with input from the youth • The recruitment of a **care manager who can relate well to youth** in a non-judgmental manner • The inclusion of **motivational interviewing training for the DCM** to help engage youth • The provision of **written treatment plans** to facilitate communication between the youth, parent, PCP, and DCM • Regular DCM **contact with the parent** to discuss any concerns • The development of **adolescent-specific treatment algorithms** that are consistent with the Guidelines for Adolescent Depression in Primary Care and GHC Guidelines for Adolescent Depression Treatment • Additional emphasis on **combination treatment** for youth who are not improving on Step 1 treatment

Youth randomized to the ACCT intervention will be scheduled for a pre-treatment education and engagement session with the DCM in the primary care clinic. At the end of the education and engagement session, the DCM will give youth (with parent input) the choice of Step 1 treatment: brief Cognitive Behavioral Therapy (CBT) or antidepressant medication.

Antidepressant treatment advancement will be guided by the Texas Children's Medication Algorithm Project Major Depressive Disorder Algorithm.[99] Youth who elect medication treatment will have weekly

telephone or in-person follow-up during the acute phase. Brief CBT will be conducted weekly in the primary care office using the STAND protocol developed by Greg Clarke and colleagues.

The aim of acute treatment will be remission, but realistically, we anticipate that many patients will achieve response but not remission. Youth will enter the continuation phase when they either reach remission (score of <5 on the PHQ-9 and at least a 50% decrease in baseline PHQ-9 score) or the treatment team feels that there has been a reasonable clinical response and it is unlikely further treatment increases will improve the patient's symptoms further. Youth in the continuation phase will have monthly in-person or telephone contacts with the DCM until the end of the 12-month intervention. During these contacts, the DCM will monitor depressive symptoms with the PHQ-9 and reinforce CBT skills for youth who received psychotherapy and adherence to antidepressants for youth on medications.

Usual Care Content: In the usual care condition (UC), the parent and youth and the PCP will receive a letter informing them of study assignment and the concern for depression along with a list of resources and the pamphlet, *A Family Guide: What Families Should Know about Adolescent Depression and Treatment Options* published by the National Alliance on Mental Illness. The intervention consent form, obtained prior to randomization, will include consent to notify the PCP of baseline screening results. Parents will be encouraged to set up an appointment for their child to talk with their PCP for further evaluation and to proceed using the services available to them. Based our previous studies of adults in the [102, 103] and other national samples[88], the low levels of detection and treatment in our recent epidemiologic study[80], and low levels of treatment in the control group for the YPIC study[7]; we anticipate that 50% or less of the UC patients will receive active depression treatment over the follow-up period and that a much smaller percentage will receive guideline concordant treatment. The treatments actually received will be monitored using GHC automated pharmacy and utilization data. We will also ask youth about the nature and frequency of mental health care received at the follow-up assessments. Because this is an effectiveness study, treatment decisions for UC patients will be left to the PCP and may include pharmacologic management, referral to GHC specialists, mental health services, or local resources. Patients in GHC can also self refer to GHC mental health services.

As part of the intervention, all PCPs will have received an educational session regarding the treatment of adolescent education and copies of adolescent treatment guidelines. Studies have demonstrated that notification of the patients depression status to the primary care physician has no measurable impact on the adequacy of treatment or patient outcomes[88, 102] It is possible that implementing the intervention will have positive effects on recognition and management of depression among adolescents in the practices of participating physicians. We have assessed the extent of such "spill-over" effects in our previous studies and found them to be minimal.[88, 95, 102, 104-106]

Follow-up Assessments:

For all patients enrolled in the trial, telephone follow-up assessments will be carried out at 6 & 12 months post-baseline by research assistants blind to group assignment. Subjects will be instructed not to divulge information related to their treatments with evaluators. Because it is not possible to blind the research participants, the interviewers will be asked whether they learned the patient's group assignment and to guess the study group assignment at the end of each interview. This will be monitored to assess whether blinding was maintained. Our experience in similar trials has been that research assistants conducting interviews infrequently learn patients' group assignment.

We anticipate that follow-up surveys will take about 15-30 minutes and will include a reassessment of depressive symptoms (using the Children's Depression Rating Scale (CDRS-R)), functional impairment, interval treatment. Youth participants will be paid $10 for their time to complete the 6, and 12-month surveys. To minimize loss to follow up, we will obtain phone numbers of two additional contacts from each parent to use in case the family moves. We will also obtain email addresses to check in quarterly with study participants, and will follow-up via phone to re-confirm contact info if e-mail bounces back.

Analytic Plan:

The ROAD intervention (acute and continuation phase) lasts up to 12 months post-baseline. We plan to examine the primary acute and continuation outcomes at three time points: baseline, 6, and 12 months post-baseline. Intent-to-treat analyses will be employed. We will report data describing the extent to which the intended treatments were administered and information relevant to characterizing care received by youth in the Usual Care group.

Data from GHC automated data systems will be used to assess differences between respondents and non-respondents at the enrollment phase of the study. The ROAD intervention and Usual Care groups will be compared on a wide range of baseline variables to assess whether the two groups are balanced at baseline.

Analysis of Specific Aims

Intervention effects: We will use mixed models to test for the effect of the ROAD intervention on depressive symptoms as measured by the Child Depression Rating Scale (CDRS-R) (Primary outcome) and on functional status as measured by the Columbia Impairment Scale (CIS) (Secondary outcome). Before performing the mixed models, we will use general linear models to make cross-sectional comparisons between the study groups at 6 and 12 months respectively. Mixed model analyses will use all available data collected at baseline, 6 and 12 months post-baseline, including patients with varying amounts of follow-up data. We will include time as a random effect in the models to account for the within-subject correlations. In the mixed models, we will be testing the impact of the main effects of treatment group, time, and group by time interaction on depressive symptoms and functional impairment. If necessary, we will control for other covariates of interest, such as demographic variables and prior history of depression. We will also analyze dichotomous measures of response to treatment (the percentage of youth with $\geq$50% reduction in baseline CDRS-R as well as percent reaching remission on the PHQ-9) via logistic regression models.

Specific Aim 2: The primary dependent measures in the analyses are: 1) receipt of a minimally effective dose of pharmacotherapy (defined as the low end of the dosage range guidelines from the Texas Children's Medication Algorithm Project) for at least 3 months and 2) having attended 4 or more mental health therapy sessions or treatment at 6 and 12 months. We will use logistic regression models to determine whether the ROAD subjects are more likely than UC subjects to have met each of the specific evidence-based treatment criteria outlined above.

Missing Data: We plan to record into our protocol reasons for missing data from dropout, such as side effects, feeling better or worse, or onset of another psychiatric disorder. If non-response rates are less than nominal levels (5%), mixed effects models using maximum likelihood procedures will be used to reduce the effects of missing data. If the missing rates exceed nominal levels (5%), or differ for usual care and intervention groups, and the missingness is likely to be MAR (missing at random) based on the reasons for missing, we will perform multiple imputation to impute the missing values. The regression models will include all relevant variables to ensure that the imputation process utilizes as much observed information as possible. The analyses based on the imputed data will be compared with conclusions obtained from the complete cases to examine the potential impact of missing data. If we believe the data are not MAR and the nature of the dropout process cannot be discerned, we will carry out sensitivity analyses to evaluate how the inferences respond to different model assumptions.